Uric Acid and Preeclampsia

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Increased uric acid level is a key clinical feature of preeclampsia; higher levels correlate with significant maternal and fetal morbidity and mortality. The cause of hyperuricemia and its specific role in the pathogenesis of preeclampsia, however, remain unclear. Although uric acid has been shown to roughly parallel the severity of the maternal syndrome, it has not been useful in predicting the development of preeclampsia. Nevertheless, there have been recent data supporting a pathogenic role potentially in the hypertension and endothelial cell dysfunction of preeclampsia. This article reviews our current understanding of hyperuricemia in the setting of preeclampsia, and highlights the hypothesis that hyperuricemia may contribute to vascular damage in preeclampsia.
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The association of hyperuricemia with preeclampsia has been known since 1917[1]; the relationship of the degree of hyperuricemia and severity of disease has been known since at least 1934.[2] What is not clear is the role that uric acid plays in the pathophysiology of preeclampsia—whether it is a marker of disease or whether it actively takes part in the pathogenesis of disease.

Although hyperuricemia does not predict the development of preeclampsia, the severity of hyperuricemia has been observed to correlate with maternal and fetal morbidity and severity of the renal lesion, and to be inversely proportional to birth weight.[3-6] Most often, increase of the uric acid level precedes the onset of proteinuria and hypertension, suggesting a possible causal role for uric acid.[7] Recently, because of uric acid's role in vascular damage and in oxidative stress, hyperuricemia has been evoked as a contributor to the pathogenesis of preeclampsia.[8,9] Although the renal lesion of glomerular endotheliosis is most likely caused by circulating antiendothelial factors such as soluble fms-like tyrosine kinase-1,[10] it is conceivable that uric acid may synergize with soluble fms-like tyrosine kinase-1 to induce endothelial dysfunction and the accompanying symptoms. Moreover, afferent arteriolar disease often is seen in individuals with preeclampsia and would be consistent with a uric acid–mediated effect. This might also explain why patients with preeclampsia have an increased likelihood of developing hypertension. This article reviews the evidence that uric acid may be a contributor to the overall clinical picture of preeclampsia by causing endothelial cell dysfunction and hypertension. It also may cause subsequent morbidity in women who previously have had a history of preeclampsia.

Uric Acid in Normal and Preeclamptic Pregnancies

In humans, uric acid is the final product of purine metabolism: the result of hypoxanthine and xanthine degradation by xanthine oxidase (XO) and xanthine dehydrogenase (XD). XO produces uric acid and superoxide, and XD produces uric acid and reduced nicotinamide adenine dinucleotide.[11] Humans and great apes have higher uric acid levels than most vertebrates because they lack the enzyme uricase in the liver, which breaks down uric acid into allantoin.[12] Uric acid is 5% bound to plasma proteins in blood, but is otherwise completely filtered by the glomerulus; it then is reabsorbed (about 90% in the early proximal tubule), and secreted (about 50% of the filtered urate, via the S2 segment of the proximal tubule). Finally, it undergoes postsecretory reabsorption in the last segment of the proximal tubule.[13]

In normal pregnancy, serum uric acid level slowly decreases until about 16 weeks of gestation, secondary to plasma volume expansion, increased renal clearance, and the uricosuric effect of estrogen. For most of the 2nd trimester, the uric acid level remains stable, and then increases during

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the 3rd trimester because of increased catabolism/production.[14] The placenta in normal pregnancy is an abundant source of purines because of its high cell turnover, resulting in higher production of uric acid. Serum uric acid is also higher in normal multifetal pregnancies compared with normal singleton pregnancies, which could be explained by the fetus as an additional source of XO/XD.[15] Alternatively, increased serum uric acid levels in multifetal pregnancies could be secondary to the increased number of placentas. In a report of a patient with xanthinuria, an autosomal-recessive disorder that results in XO deficiency, serum uric acid levels were found to be increased at 32 weeks of gestation, but returned to baseline low levels by 6 weeks postpartum, suggesting a definitive role for fetal and/or placental uric acid production.[16]

The cause of hyperuricemia in preeclampsia has not been established definitively. Most evidence suggests that decreased renal clearance is the most important mechanism. However, the increase in uric acid levels is too great to be attributed to the decrease in glomerular filtration rate alone; thus, there must be decreased secretion or increased reabsorption. This phenomenon appears to be analogous to the decrease in urate clearance produced by the infusion of vasoconstrictors, such as norepinephrine,[17] and to the increase of blood uric acid level and diminution in uric acid clearance observed in glomerulonephritis.[18] In addition to decreased renal clearance, there may be increased placental production of uric acid secondary to placental ischemia and increased trophoblast shedding that lead to further purine availability for breakdown. Fetuses exposed to hypoxia (eg, because of decreased placental perfusion) have been shown to have increased serum levels of purine metabolites.[19] In preeclampsia, therefore, it is conceivable that these metabolites can cross into the maternal circulation to be degraded by maternal XO/XD. It also is possible that fetal XO/XD could act on both fetal and maternal substrate.[11]

Of note, since 1944, there have been 6 reported cases of gout attacks in women during or around the time of pregnancy, 4 of whom were felt to have primary or idiopathic gout.[20,21] Two of the 6 patients had a history of preeclampsia documented. Although these data might appear suggestive with regard to the question of whether there is a relationship between gout and preeclampsia, it is difficult to draw firm conclusions from such numbers.[20,21]

Uric Acid and Hypertension in Preeclampsia

An association of hyperuricemia with hypertension and cardiovascular disease (as well as with renal disease, obesity, insulin resistance, and diuretic use) has been noted.[12] Interestingly, women with a history of preeclampsia also have a higher risk for cardiovascular disease and hypertension later in life.[22,23]

A number of studies in animals have suggested that uric acid may play a more active part in the development of hypertension both during preeclampsia and perhaps later in life. One study involved induction of mild hyperuricemia in rats by oxonic acid (uricase inhibitor), which resulted in hypertension and afferent arteriolar thickening.[24] Rats treated with allopurinol (XO inhibitor) or benziodarone (uricosuric agent) to maintain a normal uric acid level had no hypertension or arteriolopathy. Notably, rats that were hyperuricemic, but normotensive by treatment with hydrochlorothiazide, still developed arteriolopathy. Rats given losartan or enalapril had no hypertension or arteriolopathy.[24] In another study, rats fed oxonic acid and a low-salt diet developed hyperuricemia and hypertension, as well as increased glomerular capillary pressure with thickened afferent arterioles.[25] In these rats, allopurinol prevented hyperuricemia, systemic and glomerular hypertension, and afferent arteriolopathy.[25] A third study looked at the effect of low-salt versus high-salt diets on previously hyperuricemic rats and found salt-sensitive hypertension in the latter group.[9] Another study in rats confirmed the relationship between hyperuricemia and hypertension and its prevention by allopurinol and noted, additionally, that the degree of hyperuricemia was proportional to the severity of hypertension. By histology, this study also concluded that the mechanism by which uric acid induces hypertension is not via urate crystal deposition.[26]

The mechanism of how uric acid may cause hypertension in humans has yet to be elucidated, but evidence that uric acid plays a significant role include: (1) uric acid levels correlate with plasma renin activity,[26] (2) hyperuricemia predicts the development of hypertension in the general population,[12] and (3) uric acid is an independent predictor of progression in certain renal diseases (eg, immunoglobulin A nephropathy).[12] In rats with remnant kidneys, hyperuricemia resulted in hypertension, greater proteinuria, higher creatinine levels, and more renal hypertrophy and glomerulosclerosis.[27] This particular study also showed preglomerular artery thickening. All of the changes were prevented by allopurinol and diminished by benziodarone. Increased renin and cyclooxygenase-2 (COX-2) expression were found, particularly in the preglomerular arteries. In addition, uric acid added to vascular smooth muscle cell–induced COX-2 production, which was blocked by a COX-2 or thromboxane-2 inhibitor. It also has been observed that uric acid stimulates vascular smooth muscle cell proliferation, which is blocked partially by losartan,[9,24] again indicating a mechanism possibly via the renin-angiotensin pathway.

The relationship of uric acid and nitric oxide (NO) has been explored in a number of studies. A circadian reciprocal pattern of NO and uric acid levels has been observed.[28] Infusion of allopurinol into hyperuricemic patients with congestive heart failure has been shown to improve endothelium-dependent (ie, acetylcholine co-infusion), but not endothelium-independent (eg, nitroprusside, nitroglycerin) forearm vasodilation.[29,30] These patients also had improved peak blood flow distally after treatment with allopurinol.[29] In hyperuricemic rats, juxtaglomerular renin staining has been found to be increased significantly, with a direct relationship between severity of hyperuricemia and the percentage of renin-positive glomeruli. In the macula densa of such rats, the

number of NO synthase 1–positive cells was decreased, which was not evident in allopurinol-treated rats.[26] Although hyperuricemic rats do have afferent arteriolopathy in common with preeclamptic patients, they do not have renal endotheliosis. Thus, it is possible that hyperuricemia contributes somewhat to the hypertension in the maternal syndrome, and perhaps even later in life.

Endothelial Cell Dysfunction

There is evidence to suggest a contributory role for uric acid in endothelial cell dysfunction, possibly via a proinflammatory mechanism. Vascular smooth muscle cells take up uric acid via organic anion transporters,[12] and their proliferation has been found to be mediated by activation of specific mitogen-activated protein kinases (Erk44/22, p38), induction of COX-2, increased thromboxane-2 production, and up-regulation of platelet-derived growth factor and nuclear factor κ B and activator protein-1, which leads to increased synthesis of monocyte chemoattractant protein-1.[12,31] Recently, uric acid was found to be a factor in the cytosol of dying cells that acted as a danger signal by stimulating maturation of dendritic cells that present foreign antigens and by activating T lymphocytes (augment CD8+ T-cell response). Giving allopurinol to decrease uric acid levels decreased this cytotoxic T lymphocyte priming. Interestingly, it was the injection of preformed monosodium urate crystals and not soluble uric acid that induced this danger signal response.[32]

Lipid peroxidation, occurring at low levels in normal pregnancy, is believed to be increased in preeclampsia. Uric acid's proinflammatory role conceivably could contribute to this: increased production of cytokines could cause neutrophil activation, which would result in reactive oxygen species release, which, in turn, could lead to lipid peroxides that damage endothelial cell membranes. Lipid peroxides that accumulate locally in the placenta then could circulate to distal organs, such as the liver and kidney, and cause damage.[33]

It has been thought that placental ischemia favors the XO form (which requires oxygen) over the XD form (which needs nicotinamide adenine dinucleotide), resulting in more reactive oxygen species and reactive oxygen species–derived peroxidation products. The placenta has been shown to express both XO and XD:[34] XO produces uric acid and superoxide; superoxide reacts with NO to form peroxynitrite, which is an oxidant, hence, the hypothesis that preeclamptic placentas have more oxidative stress as a result of hypoxia. A recent study, however, has observed that both XO and XD generate reactive oxygen species.[35]

Uric Acid as Oxidant or Antioxidant?

Uric acid is a known antioxidant. It is the major contributor (followed by vitamins C and E) to total radical trapping antioxidant potential in the body.[36] Its antioxidant properties include the following: metal ion chelation, reactions with oxidants (eg, hydroxyl radical and hypochlorous acid) to form more stable products (eg, allantoin), and peroxynitrite scavenging.[37] Urate protects ascorbate from oxidation by cupric ion and iron; it acts as a chain-breaking antioxidant and metal ion chelator. As an antioxidant, uric acid gives up an electron to become a urate radical, which has low oxidative potential, and is regenerated as uric acid by ascorbate (a weaker oxidant). Total antioxidant activity and uric acid increase in normal pregnancy,[38] but a number of antioxidants have been shown to be decreased in preeclampsia—notably, vitamins C, E, and A, β-carotene, and glutathione, among others.[39]

Superoxide dismutase (SOD) catalyzes the degradation of superoxide to hydrogen peroxide, but also is inactivated by hydrogen peroxide via a peroxidase reaction. In addition, SOD competes with NO for superoxide; when SOD is low, NO reacts with superoxide to form peroxynitrite, which can initiate lipid peroxidation. Uric acid has been found to prevent inactivation of Cu/Zn SOD and extracellular SOD, which also was seen in vivo in the atherosclerotic vessels of apoE-deficient (but not WT) mice that had higher uric acid levels (from being given oxonic acid).[40] Extracellular SOD activity is observed to be much less in human atherosclerotic aortic lesions compared with normal aortas. In rabbit aortas and bovine coronary arteries, inhibition of SOD causes rapid impairment of endothelium-dependent, NO-mediated vasodilation.[41-43] In this capacity, uric acid appears to be protective against oxidative damage.

On the other hand, several studies raise the question of the role of uric acid as an antioxidant: the urate radical, mediated by a constant source of peroxynitrite (from NO and superoxide reaction), may result in low-density lipoprotein oxidation (ie, once initiated by a bolus of peroxynitrite).[37,44] In another study, uric acid was found to be an antioxidant for native low-density lipoprotein, but strongly pro-oxidant for mildly (copper-) oxidized low-density lipoprotein.[45] In clinical conditions such as preeclampsia in which ascorbate concentrations are low, urate radicals (as a consequence of increased uric acid level) will accumulate and in theory may contribute to the vascular damage acting directly as a pro-oxidant.[8]

Clinical Implications

Perhaps partly for the reason that uric acid has, for the most part, been seen more as a marker of disease in preeclampsia rather than a contributor, there have been few clinical studies to assess the potential benefit of allopurinol. One particular study explored the effects on preeclamptic-like symptoms (hypertension, proteinuria, decreased uteroplacental blood flow, and decreased glomerular filtration rate) of ewes treated with pentoxifylline and allopurinol. The process by which such symptoms were induced in the ewes was fasting, which results in decreased G6PD (red blood cell antioxidant) activity, hemolysis, and, subsequently, endothelial dysfunction, vasoconstriction, and placental hypoxia. Abnormalities in renal and liver function were both diminished and delayed in the treatment group. Of 20 animals that were divided evenly into 4 groups (control; fasting: nontreated; fasting: pentoxifylline treated; and fasting: allopurinol-treated), 1 ewe from

the nontreated fasting group died in convulsions. Serum uric acid levels were similar in the control and pentoxifylline groups (4-6 μmol/L), and were lower in the allopurinol group (<2 μmol/L); but it is unclear whether there were truly significant differences between the treatment groups. Renal and liver histology were not examined in the study.[46]

To date, only one study has looked at allopurinol use in clinical preeclampsia. Women with severe preeclampsia between 24 and 32 weeks of gestation were given allopurinol 200 mg, vitamin E 800 IU, and vitamin C 1,000 mg/d for up to 14 days. The median uric acid level was 5.3, range 3.1 to 13.4 mg/dL (0.32; range, 0.19-0.81 mmol/L) in the antioxidant group; and 7.1, range 4.6 to 9.1 mg/dL (0.43; range, 0.28-0.55 mmol/L) in the control group. Although there was a trend toward prolonging pregnancy in the treatment group, this was not significant. Fetal outcome was no different in both groups, and there was no significant change in level of lipid peroxides between the 2 groups. The trial was not powered to detect differences in fetal outcome, and perhaps not enough to detect an effect on the pregnancy either. It may be that the uric acid level was not sufficiently decreased (to the optimal range).[47]

Conclusions

In preeclampsia, uric acid level has been known to be increased and to correlate with maternal and fetal morbidity, but always has been assumed to be a reflection of disease rather than a cause. The reason for its increase may be that it is a marker of oxidative stress, but there is somewhat conflicting evidence of its subsequent role(s). On one hand, uric acid has antioxidant properties that serve to protect from oxidative stress, but it also appears to contribute directly to endothelial dysfunction by its pro-inflammatory effects, as well as to hypertension during preeclampsia, and possibly later in life. The mechanism by which uric acid contributes to hypertension may be afferent arteriolopathy via the renin-angiotensin pathway, which might be related to vascular smooth muscle cell proliferation. Uric acid therefore may be protective during preeclampsia as an antioxidant, but is at the same time proinflammatory and contributes to endothelial dysfunction (via other pathways) and hypertension—ultimately with long-term ramifications. Pathologically, although the renal lesions seen in animals with hyperuricemia differ somewhat from the classically described pattern in preeclampsia, this again suggests a contributory role of uric acid rather than a direct casual role. Animal studies measuring blood pressures and renal pathologic changes in the soluble fms-like tyrosine kinase-1 model of preeclampsia at various levels of serum uric acid should help clarify if hyperuricemia indeed contributes to the vascular damage seen in this disease. It remains to be seen whether decreasing uric acid in women with preeclampsia actually impacts the course of the disease, which has not yet been shown definitively.

Notes added in Proof: A recent small study in preeclamptics reported no effect on the degree of hypertension with the usage of probenecid, although there was a statistically significant drop in uric acid levels. However, there was a significant improvement in the platelet count in the probenecid group at the end of study. (Hyperuricemia and preeclampsia: is there a pathogenic link? Schackis RC et al, Med Hypotheses, 2004: 63:239-44).

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